REMARKS

Applicants submit this response to the Office Action dated October 22, 2003. The Examiner has withdrawn the rejection of record of claims 25-35 under 35 U.S.C. § 112, second paragraph. Claims 23-38 are pending, and claims 24 and 35 are allowable.

Claims 23 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite. Applicants have amended claim 23 to clarify that it encompasses one sentence, wherein section (c) is followed by the word "and", section (d) is followed by a comma, and the last two lines beginning "wherein" relate back to section (a), (b), (c), or (d). As claim 34 depends from claim 23, the amendment to claim 23 addresses the rejection of claim 34. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claims 23, 25-34, and 36-38 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly is not enabling for any nucleic acid encoding SEQ ID NO:2 or fragments thereof, a polypeptide that is 90% identical to SEQ ID NO:2, the complement of these sequences, or polynucleotides encoding a polypeptide with up to 50 substitutions in the sequence. The Examiner reiterated that the Wands factors (In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988)) were considered in reaching this rejection. The Examiner also stated that the differential expression of SEQ ID NO:1 in prostate cancer cells relative to normal cells provides a use for SEQ ID NO:1 as a marker for abnormal prostate cells, but that this use would not encompass other polynucleotides as claimed. Other polynucleotides encoding SEQ ID NO:2 would, according to the Examiner, have use in expressing SEQ ID NO:2, but the specification allegedly has not provided a use for a polypeptide of SEQ ID NO:2. Finally, the Examiner raises issues regarding the data for inhibition of cell growth using antisense oligonucleotides directed at SEQ ID NO:1.

Applicants previously asserted that SEQ ID NO:2 is a member of the tetraspan protein family, and supplied an alignment with the previous response. The Examiner notes that it is not readily apparent whether SEQ ID NO:2 possesses the structural characteristics of tetraspan proteins.

With respect to structural homology, there are substantial and overwhelming structural homologies between SEQ ID NO:2 and tetraspan proteins, as described Serru *et al.* (Biochim Biophys Acta. 2000 Mar 16;1478(1):159-63) and Maecker *et a.l* (FASEB J. 1997 May;11(6):428-42). These references are of record in the application. As indicated in the

accompanying Declaration of Dr. Christoph Reinhard, these structural homologies include, *inter alia*: **(i)** the presence of four characteristic transmembrane domains (hydrophobic transmembrane stretches TM-1,-2,-3 and -4); **(ii)** the presence of two hydrophilic loop regions: an 18 aa hydrophilic loop region between TM-1 and TM-2 and a 116 aa loop region between TM-3 and TM-4; **(iii)** the presence of a putative N-linked glycosylation site in the large hydrophilic loop region; **(iv)** the presence of a conserved lysine just before TM-1; **(v)** the presence of conserved polar amino acids within transmembrane domains; specifically, an asparagine residue within TM-1, a glutamate residue within TM-3, and a glutamine residue within TM-4; and **(vi)** the presence of four conserved cysteine residues in the large hydrophilic loop region, including a Cys-Cys-Gly motif 38 aa downstream of TM-3, a cysteine preceded by a glycine 11 aa upstream of TM-4, and a variably-placed cysteine residue within a PXSC motif. These homologies are not shared with other protein families that also have four transmembrane domains.

The Examiner cited several publications that allegedly document the unpredictability of the relationship between sequence and function. Applicants submit that none of these publications are on point in relation to the function of the tetraspan protein, but each publication is discussed below for the sake of completeness.

The Gerhold publication (Bio Essays 18:973-981, 1996) contains a discussion of EST sequences and their current analysis as of 1996. The Examiner did not cite any particular section of this article, and the article relates only to EST analysis, not the analysis of the full coding region, such as is found in the present application. At the time of this publication, the analysis of ESTs was in an early stage and the article is directed at EST analysis and future uses. It does not relate to the issues in the present application, which involve a known family of proteins, the discovery of a new member of that family of proteins, and the characterization of that new member.

The Wells paper (J. Leuk. Bio. 61:545-550, 1997) relates to the chemokine family of proteins. This publication also relates to the use of EST sequences to discover new chemokines. Again, the Examiner has not cited any specific sections of this publication, nor has she indicated how a discussion of chemokine function relates to the characterization of a new tetraspan protein. Applicants therefore submit that this reference is not on point for the subject matter of the present application.

Russell (J. Mol. Biol. 244:332-350, 1994) discloses an analysis of side-chain contacts, secondary structure, and other features of proteins as determined by a 3D analysis. The premise of this paper is discussed in the first sentence of page 333, specifically, that proteins having no detectible sequence similarity can adopt similar 3D structures. This theme is continued in the discussion at page 345, where the authors state that the results of the study suggest that there is little in common between distantly related protein structures. Specifically, the authors state that in similar 3D structures, a common core can be formed with as few as 30% of residues. Applicants request that the Examiner point out the sections of this lengthy and detailed publication that support the Examiner's position that despite a very high degree of sequence similarity, as exists in the present tetraspan situation, one cannot predict the function of a protein. Applicants have reviewed the Russell article and have not been able to identify such a statement. In fact this article appears to make the opposite point, which is that proteins having different sequences can adopt similar 3D structures. This does not support the Examiner's point that sequence similarity may not be enough to identify a new protein.

The Attwood article (Science 290:471-473, 2000) is an analysis of bioinformatics as applied to protein function and structure. This article in fact supports Applicants' position that the sequence analysis and patterns of conservation of motifs confirms that SEQ ID NO:2 is a tetraspan protein. For example, on page 471, the legend to the Figure states that "when we look at sequences or structures together [do] the patterns of conservation that emerge (motifs) begin to provide functional clues." In the present application, Applicants have provided both sequence comparison and structure comparison, together showing the patterns of conservation that support the position that SEQ ID NO:2 is a tetraspan protein. Attwood therefore supports Applicants' position regarding the identity of the protein of SEQ ID NO:2.

The Kyrpides article is a short letter relating to annotation of whole-genome sequences. Table 1 of the publication indicates erroneous prediction of certain sequences in terms of their potential function, but all of these sequences appear to be based on whole-genome analysis. There is no indication in this publication that the predicted sequences actually represented full-length proteins, in which analysis of both the sequence and conserved regions have been performed. The Examiner has not pointed to any particular section of this paper to support her assertion that the data submitted to date for SEQ ID NO:2 is not sufficient to support its identity

as a tetraspan protein. Furthermore, a listing of 30 cases of potential genome sequence annotation conflicts does not indicate how frequently or rarely such conflicts occur.

In summary, none of the cited references support a position that sequence similarity and conserved regions are inadequate for concluding that SEQ ID NO: 2 is a tetraspan protein. In fact, some of these references do support this position. Therefore, for each paper cited, applicants request that the Examiner point out the text she is relying on, or provide an affidavit. As provided in In re Sun, 31 USPQ2d, 1455 (Fed. Cir. 1993), applicants are entitled to an Examiner affidavit regarding the grounds of rejection under 35 U.S.C. § 112, first paragraph. (37 C.F.R. § 1.104, formerly § 1.107(b) as cited in 31 USPQ2d at 1455.) The Examiner further states that in the instant case the uncertainty of function based on sequence similarity is "multiplied" since the function of SEQ ID NO:2 allegedly was based on sequence similarity with NET-4. Applicants submit that this issue has been fully addressed in the prosecution history to date, and is further confirmed by the accompanying Declaration of Dr. Reinhard, with an analysis of the conserved regions which clearly indicate that SEQ ID NO:2 represents a tetraspan protein.

Finally, the Examiner cited the publication of Serru (cited above) for the position that expression levels of known members of the tetraspan protein family are inversely correlated with metastatic potential of several cancers. The Examiner states that this seems to be the opposite effect to that observed with levels of SEQ ID NO:1 in the present specification, and that this allegedly suggests that the protein of SEQ ID NO:2 does not exhibit the functional characteristics of tetraspan proteins.

Applicants note that the Serru paper relates to the sequence and expression of seven new tetraspans. The paper states that three of these molecules have expression levels that correlated inversely with the metastatic potential of several cancers. There is no suggestion in the Serru paper that a characteristic of tetraspan proteins generally is expression levels that correlate inversely with metastatic potential. In fact, no information is provided about the role of four tetraspans in cancer, and there is no indication that these proteins are correlated in either direction with metastatic potential of cancers. Thus, Applicants' disclosure of increased expression of SEQ ID NO:1 in cancer is not at all inconsistent with the Serru paper.

Claims 23, 25-34, 37 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al., WO 99/58660. Reconsideration and withdrawal of this rejection are respectfully

requested in view of the amendment to claims. Claims 37 and 38 do not recite the "comprising" language, contrary to the statement in the office action at page 11, lines 6-9.

The Examiner has kindly indicated that claims 24 and 35 are allowable. Applicants respectfully submit that in view of the amendments, arguments, and Declaration of Christoph Reinhard filed herewith, the remaining claims are also allowable.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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